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Íris Anabela Santos Silva

# Pneumothorax in Neonates

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# Pneumothorax in Neonates

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**Trabalho efetuado sob a Orientação de:**

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**E sob a Coorientação de:**

**Dr. Gustavo Marcondes Duarte Rocha**

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NOME

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| NÚMERO DE ESTUDANTE | DATA DE CONCLUSÃO |
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DESIGNAÇÃO DA ÁREA DO PROJECTO

Pediatria - Neonatologia

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Pneumothorax in Neonates

ORIENTADOR

Maria Hercília Ferreira Guimarães Pereira Areias

COORIENTADOR (se aplicável)

Gustavo Marcondes Duarte Rocha

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# Pneumothorax in Neonates

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# Abstract

**Introduction:** Pneumothorax occurs more frequently in the neonatal period than in any other period of life and is associated with increased mortality and morbidity. Several risk factors for pneumothorax, including respiratory pathology, invasive and non-invasive respiratory support, and predictors of mortality have been described.
**Objective:** To evaluate the prevalence, to assess risk factors and to describe the clinical characteristics, management and outcome of newborn infants with pneumothorax as well as identify predictors of mortality in these newborns.
**Methods:** This retrospective case-control study included all newborns hospitalized in the NICU of Centro Hospitalar São João, Porto, Portugal, between 2003 and 2014, with the diagnosis of pneumothorax. A control group was selected among the newborns without pneumothoraces. The collected data included: demographics and perinatal data, pneumothorax characteristics, classification, treatment and clinical outcomes.
**Results:** Our study included 240 neonates (80 with pneumothoraces and 160 controls), of whom 145 were male (60.4 %). Median gestational age was 37 (24-40) weeks and median birthweight, 2612.5 (360-4324) grams. The prevalence in our NICU was 1.5 %. Pneumothorax was significantly associated with RDS ($p=0.010$) and TTN ($p<0.001$). Invasive mechanical ventilation ($p=0.016$) and $FiO2 \geq 0.4$ ($p=0.003$), were independent risk factors for the - development of pneumothoraces. The mortality rate was 13.8%. Hypotension, mechanical ventilation and thoracentesis followed by a chest tube insertion were found to be predictors of mortality in newborns having pneumothoraces, but pneumothorax was not.
**Conclusion:** Pneumothorax is relatively frequent in the neonatal intensive care unit. Its risk factors and predictors of mortality should be known in order to prevent and treat this critical situation. Pneumothorax itself was not a predictor of mortality, probably due to the adequate and prompt management used in the NICU.

**Keywords:** Pneumothorax, newborn, risk factors, mechanical ventilation, neonatal intensive care, mortality.

# Introduction

Pneumothorax occurs more frequently in the neonatal period than in any other period of life and is associated with increased mortality and morbidity. It begins with the rupture of an over-distended alveoli. The air escapes along the perivascular connective tissue sheath into the pleural space, causing pneumothorax and less commonly pneumomediastinum, pneumopericardium, subcutaneous emphysema, and pneumoperitoneum, altogether known as air leak syndromes. [1,2]

Pneumothorax is a relatively frequent critical situation in the neonatal intensive care unit. Symptomatic pneumothorax occurs in about 0.05% to 0.1% of all live births and in very low birthweight infants this rate can achieve 3.8 % to 9%. [3,4]

Several risk factors for pneumothorax have been described and include immaturity, respiratory distress syndrome (RDS), invasive and non-invasive respiratory support, chorioamnionitis, among others. For moderate-late preterm infants risk factors also include higher birth weight, male gender, and rupture of membranes longer than 24 hours. [5]

Common clinical manifestations of pneumothorax are tachypnea, flaring, hypoxemia and hypercapnea. In some cases, there is a mediastinal shift that compromises the cardiovascular system and carries a significant risk of an impaired outcome and death. Tension pneumothorax causes a rise in intrapleural pressure and subsequent lung collapse, as well as impaired venous return, systemic hypotension and cardiac arrest. It is, therefore, essential to recognize these risk infants in order to prevent and treat properly this critical situation. [1,4]

The diagnosis of pneumothorax relies on clinical judgment, transillumination and chest radiogram. [6]

The treatment of neonatal pneumothorax is not fully defined. Three approaches are the common practice in NICUs. The expectant approach for small and asymptomatic pneumothorax, and active intervention to a significant one, such as needle (14–16 G) aspiration and thoracic drainage.[7,8] Needle aspiration is an option in cases of mild to moderate pneumothorax when the infant is hemodynamically stable. In hypertensive pneumothoraces the common therapeutic approach is chest tube placement. [1]

The aim of this study was to evaluate the prevalence, to identify risk factors and to describe the clinical characteristics, management and outcome of newborn infants with pneumothorax as well as to identify the predictor factors of mortality in these newborns.

# Material and methods

This retrospective case control study included all newborns hospitalized in the NICU (a level III unit with 17 beds and 450 admissions per year and) of Centro Hospitalar São João, Porto, between 1st january 2003 and 31st december 2014, with the diagnosis of pneumothorax.

All the data were collected from the hospital electronic clinical database and medical records of the patients. A control group was selected among the newborns without pneumothoraces admitted to the NICU in the same years, gender, gestational age **(**more or less 2 weeks) and birthweight (more or less 500 g). These data includes: information regarding pregnancy and delivery (gestational age, multiple births, type of deliver), gender, birth weight, Apgar score at 1 and 5 minutes, the need of resuscitation, antenatal corticotherapy, need for

surfactant, oxygen therapy, nasal continuous positive airway pressure (NCPAP), conventional mechanical ventilation (CMV) and high frequency oscillation ventilation (HFOV) use .

Pneumothorax characteristics were also obtained (day of life and the duration of the pneumothorax) and classified as spontaneous (primary or secondary), iatrogenic (positive airway pressure or surgery), hypertensive and persistent. Data about treatment, neonatal morbidity and mortality were also collected. Pneumothoraces were diagnosed by chest radiography and the type of pneumothorax was assessed according to clinical setting and medical history. [1]

Gestational age was assessed by post-menstrual age, ultrasound examination or the New Ballard Score (in the absence of obstetrical indexes). [9, 10] Small for gestational age was defined as a birth weight below the 3rd centile of Fenton`s growth charts. [11] Our NICU has a protocol for positive pressure ventilation that includes different ventilatory strategies according to different lung diseases and favors the use of permissive hypercapnea. For the very low birth weight infants NCPAP just after birth is the preferable mode of ventilation. [12] NCPAP is done using Infant Flow (Pulmocor, USA), for invasive mechanical ventilation we use Babylog (Drager, Germany). HFOV is performed as rescue ventilation (Sensor Medics®, USA).

Sepsis was considered in the presence of a positive blood culture, combined with clinical and laboratory parameters. [13] Intraventricular hemorrhage (IHV) was defined according to Papile [14] and Volpe [15] (before and after 2010, respectively), intraventricular bleeding with ventricular dilatation is classified as IHV 3 and with parenchymal involvement as IHV 4. Retinopathy of prematurity (ROP) was diagnosed and classified according to the International Classification of Retinopathy of Prematurity revised. [16] Patent ductus arteriosus (PDA) was diagnosed according to SIBEN consensus. [17] Necrotizing enterocolitis (NEC) was defined by clinical findings and radiological features, according to the modified Bell criteria. [18] Cystic periventricular leukomalacia (PVL) was diagnosed by ultrasound. [19]

Respiratory distress syndrome was defined based on the European guidelines [20] and bronchopulmonary dysplasia (BPD) according to the NIH Consensus definition. [21] Transient tachypnea of the newborn (TTN) was diagnosed according to the criteria of Machado and Fiori. [22] Pneumonia was diagnosed based on combination of clinical, radiological and laboratory parameters. [23] Meconium aspiration syndrome (MAS) was characterized based on Shahed A. Criteria. [24] Pulmonary hypoplasia (PH) was defined according on clinical, radiologic, and pathologic criteria. [25]

Hypotension was defined according Cayabyab et al. [26]

The statistical analysis was performed using SPSS for Windows, version 23. Categorical variables were evaluated by absolute and relative frequencies and continuous variables were characterized by median (minimum-maximum). All variables were compared between neonates with (cases) or without (controls) pneumothorax. Chi-Squared or Fisher's exact test were used to compare categorical variables and Mann Whitney-U test (non-parametric test) to compare continuous variables. Risk factors for pneumothorax were evaluated by a multivariate analysis by logistic regression. Statistically significance was considered for a p value less than 0.05.

# Results

Our study included 240 neonates (80 with pneumothoraces and 160 controls), of whom 145 were males (60.4 %). Their median gestational age was 37 (24-40) weeks and the median birthweight was 2612.5 (360-4324) grams. The prevalence in our NICU was 1.5 %. .The analysis of demographic and perinatal data of both groups showed statistically significant

differences in Apgar score at 5th minute ($p = 0.002$) and in resuscitation at birth ($p < 0.001$), Table 1.

Table 2 describes the characterization and treatment of pneumothoraces. They were spontaneous (primary or secondary to lung disease) in 46 (57.5%) neonates and iatrogenic in 34 (42.5%). Fifty seven (71.3%) were hypertensive and 2 (2.5%) persistent. We observed 37 (46.3%) pneumothoraces in the right lung, 35 (43.8%) in the left and 8 (10%) were bilateral. Oxygen therapy was done in 68 (85%) neonates, NCPAP in 15 (18.8%) and IMV in 60 (75%) newborns. Thoracentesis was performed in 10 (12.5%) pneumothoraces, but 7 of them also had to be drained. To treat the pneumothoraces, 57 (71.3%) neonates needed drains and 3 (3.8%) thoracentesis.

In Table 3 we present the clinical and management data in cases and controls. There were statistically significant differences between both groups concerning respiratory pathology (pneumonia, MAS, RDS, pulmonary hypoplasia, transient tachypnea of the newborn). IVH $\geq$3 grade, PDA, cystic PVL and hypotension were also more frequent in newborns having pneumothorax. Use of oxygen therapy ($p<0.001$), NCPAP ($p<0.001$) and mechanical ventilation ($p<0.001$) also revealed a significant increase in pneumothorax cases. Statistical significance between the two groups was also found for $FiO2 \geq 0.4$ ($p < 0.001$). The association with pneumothorax was found for major congenital malformations: congenital cardiopathy (CHD) and diaphragmatic hernia. The average of days of hospitalization was 9.5 in pneumothorax group and 4 in controls ($p<0.001$). The prevalence of death was 24 (30%) in cases and 9 (5.6%) in controls ($p < 0.001$).

The two respiratory pathologies, RDS (OR 3.512, 95% CI 1.353-9.118, p=0.010) and TTN (OR 8.677, 95% CI 2.752-27.354, $p<0.001$) were significantly associated with pneumothorax. Mechanical ventilation was also significantly associated with pneumothorax (OR 3.824, 95% CI 1.285-11.376, $p<0.016$), as was $FiO2 \geq 0.4$ (OR 5.614, 95%CI 1.828-17.238, p=0.003), Table 4. Pneumothorax was not identified as a predictor of death OR 1.284, 95% CI 0.409-4.032, p=0.669). Hypotension, thoracentesis and mechanical ventilation were found to be predictors of death in newborns with pneumothoraces, Table 5.

# Discussion

In this study we aimed to compare clinical characteristics between neonates with and without pneumothoraces and to identify risk factors of pneumothoraces and predictors of death in these patients.

As expected, there were no significant differences between cases and controls, for gender, gestational age and birth weight. Statistically significant differences in Apgar score at 5th minute occurred due to the need of resuscitation at birth, which was found to be a risk factor ($p < 0.001$). According to clinical practice, the use of invasive ventilation with endotracheal intubation in neonatal resuscitation is less and less used and replaced by noninvasive ventilation with the minimum effective pressure. [12] The type of delivery had no influence in pneumothorax occurrence, results that are consistent with others. [2, 27] Antenatal steroids use wasn´t associated with pneumothorax (p=0.976), data according with other studies. [28]

The treatment of pneumothorax is not fully defined. In this study we had 80 pneumothoraces, spontaneous in 46 (57.5%) neonates and iatrogenic in 34 (42.5%), but only 68 (85%) received oxygen therapy, because pneumothoraces with very small size in chest x-ray solved spontaneously. As described in literature, other option for treatment is the expectant management for non hypertensive pneumothoraces in patients who are ventilated [3], and this

approach was done in 15 (18.8%) neonates with NCPAP and in 60 (75%) with CMV. The use of needle aspiration and chest tube are common options for the treatment. Thoracentesis was made in 10 (12.5%) pneumothoraces, however this treatment wasn´t effective in seven of them. So, thoracentesis only treated 3 (3.8%) non hypertensive pneumothoraces. It is known that, frequently, neonates treated with needle aspiration, can require subsequent chest-tube insertion. [29] In our study 57 (71.3%) neonates needed drains to be effectively treated.

As described in Table 3, there was a statistical significant difference between cases and controls concerning respiratory pathology. When adjusted by multivariate analyses, RDS showed an OR=3.512 and TTN was OR=8.677, which means that they were positively related with pneumothorax, results comparable with other studies. [2,28] BPD was not statistically different between the two groups, as observed in other studies. [28,30] The risk of developing pneumothorax was also increased in newborns with other pathologies (IVH ≥3 grade, PDA, cystic PVL and hypotension), showing that pneumothoraces can occur in patients with more severe diseases. As we expected the administration of surfactant was more frequent in patients with pneumothoraces, probably due to the lung pathology associated with cases. In the present study, oxygen therapy, NCPAP and CMV were related with the development of pneumothorax. Linear regression analyses indicate that neonates who received IMV had a probability 3.8 times higher to develop pneumothorax and those who received oxygen therapy with a $FiO2 \geq 0.4$ had an increased risk of pneumothorax 5.6 times higher. Terzic et al. showed that infants who needed higher FiO2 were more likely to develop pneumothorax. [28] These results suggest that high pressures in NCPAP and CMV and a high FiO2 should be avoided. Congenital heart disease and diaphragmatic hernia were also statistical significant risk factors for pneumothorax, probably because of the pathophysiological disturbances of these pathologies or their surgical repair. Congenital diaphragmatic hernia is a risk factor for pulmonary hypoplasia once it occupies space, prevents lung expansion and causes a change in the thoracic cavity. [31] Neonates with pneumothorax had a prolonged stay in NICU, an average of 9.5 days. Possibly they had more associated pathology and needed treatment.

We found that 30% of cases died comparing to 5.6% of controls ($p<0.001$). Hypotension, mechanical ventilation and thoracentesis associated with chest tube insertion were found to be predictors of mortality in newborns with pneumothoraces. These neonates had a bad prognosis since the beginning. However, in our study, pneumothorax was not identified as a predictor of mortality as had been shown by others [2,6] The good strategy and appropriate management used in the NICU was probably the explanation for this result.

The limitations of this study are to be a retrospective one, to have a small size sample and to represent a single center.

# Conclusion

Pneumothorax is relatively frequent in the neonatal intensive care unit. Its risk factors (RDS, TTN, invasive mechanical ventilation and a $FiO2 \geq 0.4$ and predictors of mortality (hypotension, mechanical ventilation and thoracentesis followed by a chest tube insertion) should be well known, in order to prevent and treat this critical situation.

Pneumothorax itself was not a predictor of mortality, probably due to the adequate and prompt management used in the NICU.

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# References


[1] Neonatal Respiratory Disorders, Moira A Crowley. Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant, J. Martin Richard, Fanaroff Avroy A., Walsh Michele C. Elsevier Saunders, 10ª edition/vol.2, pp 1113-36

[2] Duong HH, Mirea L, Shah PS, Yang J, Lee SK, Sankaran K. Pneumothorax in neonates: Trends, predictors and outcomes. J Neonatal Perinatal Med. 2014; 7(1):29-38.

[3] Kitsommart R, Martins B, Bottino MN, Sant'Anna GM. Expectant management of pneumothorax in preterm infants receiving assisted ventilation: report of 4 cases and review of the literature. Respir Care. 2012 May; 57(5):789-93.

[4] Smith J, Schumacher RE, Donn SM, Sarkar S. Clinical course of symptomatic spontaneous pneumothorax in term and late preterm newborns: report from a large cohort. Am J Perinatol. 2011 Feb; 28(2):163-8.

[5] Andrew A. Colin, Cynthia McEvoy, Robert G. Castile. Respiratory Morbidity and Lung Function in Preterm Infants of 32 to 36 Weeks' Gestational Age. Pediatrics, July 2010, 126(1): 115–128.

[6] Ozer EA, Ergin AY, Sutcuoglu S, Ozturk C, Yurtseven A. Is pneumothorax size on chest x-ray a predictor of neonatal mortality? Iran J Pediatr. 2013 Oct; 23(5):541-5

[7] MacDuff A., Arnold A., Harvey J.; et al. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. *Thorax* 2010; 65:ii18-ii31.

[8] Pocivalnik M, Meheden SV, Griesmaier E, Trawöger R, Kiechl-Kohlendorfer U, Pichler G, Reiterer F, Urlesberger B. Pneumothorax during mechanical ventilation--therapeutic options in term and preterm neonates. Klin Pediatr. 2013 Dec; 225(7):389-93.

[9] MacDonald H, American Academy of Pediatrics. Committee on F, Newborn. Perinatal care at the threshold of viability. Pediatrics. 2002; 110(5):1024-7.

[10] Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991; 119(3):417-23.

[11] Fenton, T.R. and J.H. Kim, A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr, 2013. 13: p. 59.

[12] Tavares PN, Flor-de-Lima F., Soares H., Guimarães H. Early nCPAP versus intubation in very low birth weight infants. Journal of Pediatric and Neonatal Individualized Medicine 2013; 2(2):e020201.

[13] Vergnano S., Menson E., Kennea N., et al. Neonatal infections in England: the NeonIN surveillance network, Arch Dis Child Fetal Neonatal, Ed. 2011 Jan; 96(1):F9-F14.

[14] Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978; 92(4):529-34.

[15] Volpe JJ. Neurology of the newborn. 4th ed. Philadelphia: W.B. Saunders; 2001. xiii, 912 p. p.

[16] International Committee for the Classification of Retinopathy of, P., The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol, 2005. 123(7): p. 991-9.

[17] Golombek SG, Sola A, Baquero H, Borbonet D, Cabanas F, Fajardo C, Goldsmit G, Lemus L, Miura E, Pellicer A, Perez JM, Rogido M, Zambosco G, van Overmeire B, Primer Grupo de Consenso Clinico S. First SIBEN clinical consensus: diagnostic and therapeutic approach to patent ductus arteriosus in premature newborns. Anales de pediatria. 2008; 69(5):454-81.

[18] Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am. 1986; 33(1):179-201.

[19] Kuk, J.Y., et al., Optimal time interval between a single course of antenatal corticosteroids and delivery for reduction of respiratory distress syndrome in preterm twins. Am J Obstet Gynecol, 2013, 209(3): p. 256 e1-7.

[20] Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Vento M, Halliday HL, European Association of Perinatal M. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology. 2013; 103(4):353-68.

[21] Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001; 163(7):1723-9.

[22] Machado LU, Fiori HH, Baldisserotto M, Ramos Garcia PC, Vieira AC, Fiori RM. Surfactant deficiency in transient tachypnea of the newborn. J Pediatr. 2011; 159(5):750-4.

[23]Nissen, M.D., Congenital and neonatal pneumonia. Paediatr Respir Rev, 2007; 8(3): p. 195-203.

[24] Shahed A., Dargaville P., Ohlsson A., Soll R. Surfactant for meconium aspiration syndrome in term and late preterm infants, Cochrane Database Syst Rev. 2014, december 2014;12:CD002054.

[25] Laudy J., Tibboel D., Robben S., Krijger R., Ridder M., Wladimiroff J. Prenatal Prediction of Pulmonary Hypoplasia: Clinical, Biometric, and Doppler Velocity Correlates. Pediatrics, February 2002, volume 109 / issue 2.

[26] Cayabyab R., McLean C W and Seri I. Definition of hypotension and assessment of hemodynamics in the preterm neonate. Journal of Perinatology (2009) 29, S58–S62.

[27] Basua S., Kumara A, Gupta AK. Complications associated with neonatal resuscitation. Resuscitation, 2009, 80:4-5.

[28] Terzic S., Heljic S., Panic J., Sadikovic M., Maksic H. Pneumothorax in premature infants with respiratory distress syndrome: focus on risk factors. Journal of Pediatric and Neonatal Individualized Medicine 2016; 5(1):e050124.

[29] Litmanovitz I, Carlo WA. Expectant management of pneumothorax in ventilated neonates. Pediatrics. 2008; 122(5): e975-9.

[30] Bhatia R, Davis PG, Doyle LW, Wong C, Morley CJ. Identification of pneumothorax in very preterm infants. J Pediatr. 2011;159(1):115-20.e1.

[31] Delgado-Peña YP, Torrent-Vernetta A, Sacoto G, de Mir-Messa I, Rovira-Amigo S, Gartner S, Moreno-Galdó A, Molino-Gahete JA, Castillo-Salinas F. Pulmonary hypoplasia: An analysis of cases over a 20-year period. An Pediatr (Barc). 2015 Nov 25. pii: S1695-4033(15)00405-1.

**Table 1. Demographic and perinatal data**

| | Total (n=240) | Cases (n=80) | Controls (n=160) | P |
|---|---|---|---|---|
| **Gender, n (%)** | | | | |
| Male | 145 (60.4) | 50 (62.5) | 95 (59.4) | 0.641* |
| Female | 95 (39.6) | 30(37.5) | 65(40.6) | |
| **Gestational age (weeks), median (min-max)** | 37 (24-40) | 37 (24-40) | 37 (24-40) | 0.948¥ |
| **Gestational age (weeks), n (%)** | | | | |
| < 37 | 117 (48.8) | 39 (48.8) | 78 (48.8) | 0.999* |
| <28 | 29 (12.1) | 9 (11.3) | 20 (12.5) | 0.779* |
| **Birth weight (g), median (min-max)** | 2612.5 (360-4324) | 2588 (360-4260) | 2642.5 (450-4324) | 0.836¥ |
| **Parity, n (%)** | | | | |
| Single | 208 (86.7) | 65 (81.3) | 143 (89.4) | 0.081* |
| Multiple | 32 (13.3) | 15 (18.2) | 17 (10.6) | |
| **Antenatal steroids, n (%)** | 72(30) | 24 (30) | 48 (30) | 0.976* |
| Full cycle | 53 (22.1) | 18 (22.5) | 35 (21.9) | 0.912* |
| **Type of Delivery, n (%)** | | | | |
| Vaginal | 129 (53.8) | 36 (45) | 93 (58.1) | 0.055* |
| C-section | 111 (46.3) | 44 (55) | 67 (41.9) | |
| **Apgar Score, n (%)** | | | | |
| 1st min <7 | 76(31.7) | 32(40) | 44(27.5) | 0.050* |
| 5th min <7 | 27 (11.3) | 16 (20) | 11 (6.9) | **0.002*** |
| **Resuscitation at birth, n (%)** | 64 (26.7) | 37 (46.3) | 27 (16.9) | **<0.001*** |
| Endotracheal Intubation | 31(48.4) | 22 (59.5) | 9 (33.3) | **0.039*** |

* Chi-square test, ¥ Mann-Whitney U test.; p<0.05, statistical significance

**Table 2. Characterization and treatment of cases (n=80)**

| **A. Characterization of Pneumothoraces** | |
|---|---|
| **Spontaneous, n (%)** | 46 (57.5) |
| Primary | 6 (13) |
| Secondary to lung disease | 40 (87) |
| **Iatrogenic, n (%)** | 34 (42.5) |
| Positive Pressure Ventilation | 32 (94.1) |
| During surgery | 2 (5.9) |
| **Laterality, n (%)** | |
| Right | 37 (46.3) |
| Left | 35 (43.8) |
| Bilateral | 8 (10) |
| **B. Treatment of Pneumothoraces** | |
| **Oxygen therapy, n (%)** | 68 (85) |
| FIO2 after pneumothorax, median (min-max) | 0.4 (0.21-1) |
| Days, median (min-max) | 4 (1-83) |
| **NCPAP, n (%)** | 15 (18.8) |
| Days, median (min-max) | 9 (1-32) |
| **Mechanical Ventilation, n (%)** | 60 (75) |
| Days, median (min-max) | 4 (1-48) |
| **Thoracentesis, n (%)** | 3 (3.8) |
| **Drain, n (%)** | 57 (71.3) |
| Days, median (min-max) | 3(1-21) |

NCPAP: nasal continuous positive airway pressure

**Table 3. Clinical and management data**

| | Total (n=240) | Cases (n=80) | Controls (n=160) | P |
|---|---|---|---|---|
| **Pneumonia, n (%)** | 6 (7.5) | 6 (7.5) | 0 | **0.001**[**] |
| **Meconium aspiration syndrome, n (%)** | 3 (1.3) | 3 (3.8) | 0 | **0.036**[**] |
| **Respiratory distress syndrome, n (%)** | 35 (14,6)) | 24 (30) | 11 (6.9) | **<0.001**[*] |
| **Severe pulmonary hypoplasia, n (%)** | 7 (2.9) | 7 (8.8) | 0 | **<0.001**[*] |
| **Transient tachypnea of the newborn, n (%)** | 16 (6.7) | 10 (12.5) | 6 (3.8) | **0.010**[*] |
| **Sepsis, n (%)** | 48 (20) | 16 (20) | 32 (20) | 0.999[*] |
| **Bronchopulmonary dysplasia, n (%)** | 9 (3.8) | 5 (6.3) | 4 (2.5) | 0.999[**] |
| **Intraventricular hemorrhage ≥3, n (%)** | 10 (4.2) | 8 (10) | 2 (1.3) | **0.003**[**] |
| **Retinopathy of prematurity ≥2, n (%)** | 6 (2.5) | 2 (2.5) | 4 (2.5) | 0.999[**] |
| **Necrotizing enterocolitis ≥2, n (%)** | 10 (4.2) | 3 (3.8) | 7 (4.8) | 0.999[**] |
| **Patent ductus arteriosus, n (%)** | 16 (6.7) | 9 (11.3) | 7 (4.4) | **0.044**[*] |
| **Cystic periventricular leukomalacia, n (%)** | 6 (2.5) | 6 (7.5) | 0 | **0.001**[**] |
| **Hypotension, n (%)** | 18 (7.5) | 12 (15) | 6 (3.8) | **0.002**[*] |
| **Vasopressors, n (%)** | 16 (6.7) | 11 (13.8) | 5 (3.1) | **0.002**[*] |
| **Surfactant, n (%)**<br>Doses, median (min-max) | 41 (17.1)<br>1 (1-4) | 30 (37.5)<br>1 (1-3) | 11 (6.9)<br>2 (1-4) | **<0.001**[*]<br>**<0.001**[¥] |
| **Oxygen therapy, n (%)** | 85 (35.4) | 59 (73.8) | 26 (16.3) | **<0.001**[*] |
| Days of oxygen, median (min-max) | 2 (1-75) | 2 (1-25) | 5 (1-75) | **<0.054**[¥] |
| **FiO2, median (min-max)** | 0.21 (0.21-1) | 0.4 (0.21-1) | 0.21 (0.21-1) | **<0.001**[¥] |
| **FiO2 ≥ 0.4, n (%)** | 54 (22.5) | 43 (53.8) | 11 (6.9) | **<0.001**[*] |
| **NCPAP, n (%)**<br>Days, median (min-max) | 51 (21.3)<br>2 (1-35) | 28 (35)<br>1 (1-15) | 23 (14.4)<br>3 (1-35) | **<0.001**[*]<br>**0.006**[¥] |
| **Mechanical Ventilation, n (%)**<br>Days, median (min-max) | 64 (26.7)<br>1.5 (1-25) | 47 (58.8)<br>2 (1-25) | 15 (9.4)<br>1 (1-24) | **<0.001**[*]<br>0.141[¥] |
| **PIP max, median (min-max)** | 24.5 (0-40) | 25 (16-40) | 22 (0-35) | 0.161[¥] |
| **PEEP max, median (min-max)** | 4 (0-7) | 4 (2-6) | 4 (0-7) | 0.582[¥] |
| **Thoracic congenital malformation, n (%)**<br>Congenital cardiopathy<br>Diaphragmatic hernia<br>Esophageal atresia | 25 (10.4)<br>11 (4.6)<br>9 (3.8)<br>5 (2.1) | 23 (28.8)<br>11 (13.8)<br>9 (11.3)<br>3 (3.8) | 2 (1.3)<br>0<br>0<br>2 (1.3) | **<0.001**[**]<br>**<0.001**[**]<br>**<0.001**[**]<br>0.337[**] |
| **Days of hospitalization, median (min-max)** | 5 (1-167) | 9.5 (1-167) | 4 (1-149) | **<0.001**[¥] |
| **Death, n (%) (3)** | 33 (13.8) | 24 (30) | 9 (5.6) | **<0.001*** |

[*]Chi-square test; [**] Fisher's exact test; [¥] Mann-Whitney U test; p <0.05, statistical significance
NCPAP: nasal continuous positive airway pressure; PIP: Positive inspiratory pressure; PEEP: Positive end expiratory pressure.

**Table 4 – Risk factors of pneumothorax**

| | OR* | 95% CI | p |
|---|---|---|---|
| Respiratory distress syndrome | 3.512 | 1.353-9.118 | 0.010 |
| Transient tachypnea of the Newborn | 8.677 | 2.752-27.354 | <0.001 |
| FiO2≥ 0.4 | 5.614 | 1.828-17.238 | 0.003 |
| Mechanical ventilation | 3.824 | 1.285-11.376 | 0.016 |

OR- odds ratio, CI- confidence interval; p <0.05, statistical significance (Multivariate analysis)
* Logistic regression;

**Table 5 – Predictors of mortality in newborns with pneumothoraces**

| | OR* | 95% CI | p |
|---|---|---|---|
| Pneumothorax | 1.284 | 0.409-4.032 | 0.669 |
| Hypotension | 6.165 | 1.702-22.327 | 0.006 |
| Thoracentesis and chest tube insertion | 8.195 | 1.280-52.478 | 0.026 |
| Mechanical ventilation | 29.551 | 8.257-105.765 | <0.001 |

OR- odds ratio, CI- confidence interval; p <0.05, statistical significance (Multivariate analysis)
* Logistic regression

# Agradecimentos

À Professora Hercília Guimarães, pelo apoio incansável e orientação fundamentais para a realização desta dissertação.

Ao Dr. Gustavo Rocha, co-orientador, pela orientação científica e contribuição no desenvolvimento deste projeto.

À Dra. Filipa Flôr-de-Lima, pelo apoio imprescindível na realização da análise estatística dos dados.

A todos os que me apoiaram ao longo deste projecto.

# ANEXOS

Parecer da Comissão de Ética para a Saúde e
Autorização do Conselho de Administração do
Centro Hospitalar de S. João

Normas da revista

Journal of Pediatric and Neonatal Individualized Medicine

(JPNIM)

Direcção Clínica
3/6/15

CES 154-15

**Exmo. Senhor**
**Presidente do Conselho de Administração do**
**Centro Hospitalar de S. João – EPE**

AUTORIZADO
CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 19 JUN 2015
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(Prof. Doutor António Ferreira)
Directora Clínica | Enfermeira Directora | Vogal Executivo | Vogal Executivo
(Dra. Margarida Tavares) | (Enfermeira Eurídice Portela) | (Dr. João Oliveira) | (Dr. Amaro Ferreira)

**Assunto:** Pedido de autorização para realização de estudo/projecto de investigação

**Nome do Investigador Principal:** Íris Anabela Santos Silva

**Título do projecto de investigação:** Pneumothorax in Neonates

Pretendendo realizar no(s) Serviço(s) de Pediatria do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 04 / Maio / 2015

O INVESTIGADOR/PROMOTOR

Íris Anabela Santos Silva

## 7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☑
NÃO APLICÁVEL ☐

## 8. TERMO DE RESPONSABILIDADE

Eu, Íris Anabela Santos Silva,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 29 / Abril / 2015

Íris Anabela Santos Silva

O Investigador Principal

*PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO*

emitido na reunião plenária da CES de 15 / Maio / 2015

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor
Presidente da Comissão

# COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO E DA FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

## Parecer

**Projecto**: Pneumothorax in neonates

**Nome do Investigador Principal**: Íris Anabela Santos Silva

**Serviço onde decorrerá o Estudo**: Serviço de Pediatria do Centro Hospitalar de S. João

Objectivo e Pertinência do Estudo:

Com este projeto de investigação, de natureza retrospectiva, pretende-se avaliar a incidência do pneumotórax em recém-nascidos, estratificada pela idade gestacional, e estudar possíveis factores de risco, comparando com controlos. Cumpre ainda aos objectivos analisar a mortalidade associada.

Os dados pretendidos recolher e analisar estão devidamente assinalados e enquadram-se nos objectivos do estudo. Será a investigadora a aceder ao processo clínico, por mediação do Elo de Ligação, e não directamente.

A Senhora Directora de Serviço deu o respectivo aval à realização do estudo.

Benefício/risco: NA

Respeito pela liberdade e autonomia do sujeito de ensaio: NA.

Confidencialidade dos dados: É indicado que será preservada a confidencialidade dos dados a recolher, por reserva da respectiva identidade.

Elo de ligação: Prof.ª Hercília Guimarães

Indemnização por danos: NA

Continuação do tratamento: NA

Propriedade dos dados: Estão previstos critérios de publicação dos resultados a obter.

Curriculum do investigador: Adequado ao perfil da investigação.

Data previsível da conclusão do estudo: 30 Setembro 2015.

Conclusão: Os objectivos do estudo justificam a sua realização, pelo que proponho à CES um parecer favorável à sua realização.

Porto e H.S.João, 2015-05-14

O relator

Doutor Filipe Almeida

# Journal of Pediatric and Neonatal Individualized Medicine (JPNIM)

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